CUMULATIVE OTOTOXICITY OF AMINOGLYCOSIDES

IN CYSTIC FIBROSIS PATIENTS: AN EVALUATION BY

HIGH FREQUENCY AUDIOMETRY

by

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FINAL READING APPROVAL

TO THE DOCTOR OF PHARMACY COMMITTEE OF THE UNIVERSITY OF UTAH COLLEGE OF PHARMACY:

I have read the clinical research report of Teresa Isabelle McRorie in its final form and have found that 1) its format, citations, and bibliographic style are consistent and acceptable; 2) its illustrative materials including figures, tables and charts are in place; and 3) the final manuscript is satisfactory to the Supervisory Committee and is ready for submission to the Doctor of Pharmacy Committee.

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UNIVERSITY OF UTAH COLLEGE OF PHARMACY

SUPERVISORY COMMITTEE APPROVAL

of a clinical research project submitted by

Teresa Isabelle McRorie

We, the undersigned, have read this clinical research project report and found it to be of satisfactory quality for a Doctor of Pharmacy Degree.

Date   Chairman, Supervisory Committee

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This project is dedicated to my parents, Martha and Chester McRorie, out of my deepest love and respect.

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INTRODUCTION

Aminoglycosides were first introduced in 1945 with the development of streptomycin. Almost immediately the first case reports of ototoxicity were described in patients receiving the drug for tuberculosis.[1] The potential to produce both vestibular and auditory toxicity became widely known effects of the use of all of the subsequently developed aminoglycosides. Although this toxicity has been known for greater than forty years, understanding the factors that influence the incidence and extent of ototoxicity still require extensive study. It remains unclear what places an individual most at risk for developing this toxicity. Exactly which parameters to monitor are debated, and the utility of such monitoring questioned.[2] Much attention has been placed on measuring aminoglycoside serum concentrations and establishing a therapeutic range to both ensure efficacy and prevent both ototoxicity and nephrotoxicity.

The state of the art in monitoring ototoxicity stands in sharp contrast to the monitoring of nephrotoxic damage, where serum creatinine, creatinine clearances and serum concentrations of the agent are routinely measured. Measurements of effects of these drugs on both cochlear and vestibular function are not routinely utilized.

Part of the reason for this is that tests needed to detect otological damage are both time consuming and often logistically impossible in critically ill patients. Furthermore, previously, there has not been a tool that is sensitive enough to always detect early ototoxicity. To illustrate this point some background information concerning the effects of aminoglycosides on the ear are necessary. Only cochlear toxicity will be discussed as this is the focus of the present study.

Cochlear toxicity is thought to be a result of aminoglycoside damage to the outer and inner sensory hair cells of the organ of Corti. Histologically, this damage has been described in both guinea pigs and humans as occurring initially at the base of the cochlea and moving toward the apex as the damage progresses.[3,4] Clinically this is represented by elevation of hearing thresholds in the high-frequencies with a progression into the lower frequencies. Traditionally in human audiology, low to mid frequencies are designated as those between 125 Hz and 2000 Hz. High frequencies have been considered to be 2000 Hz to 8000 Hz, and frequencies above this are extended high frequencies. Conventional audiometry evaluates frequencies from 250 Hz through 8000 Hz. In a review of the detection of ototoxicity using high-frequency auditory evaluation, Rappaport and colleagues report that the paucity of literature in this area is due to the lack of a reproducible test for pure-tone thresholds in the frequencies above 8000 Hz.[5] In audiology, a hearing threshold is defined as the lowest sensation level at which sound for a particular frequency is detected by an individual 50 percent of the time.

The precise mechanism by which aminoglycosides produce hearing loss has not been completely elucidated, although several theories have been proposed and reviewed. The most widely accepted theory is that proposed by Schacht et al. which postulates that the hair cell destruction is due to the effect on cellular membrane enzymes.[6,7] Weiner and Schacht summarized their findings in 1981 which pointed to the binding of aminoglycosides to polyphosphoinositides as the site of toxic action.[8] The polyphosphoinositides are peptides involved in the regulation of cellular membrane stability and permeability. Weiner and Schacht demonstrated that aminoglycosides alter cellular permeability and ion transport through competitive inhibition at low concentrations and noncompetitive inhibition at higher concentrations. Recently, Tachibana et al. performed binding studies with a neomycin-gold colloid complex to show histologically that neomycin binds to triphosphoinositides in the cell membranes and the nervous elements of the cochlea.[9]

This research group also reported binding of aminoglycosides to glycosaminoglycans in the connective tissues and tectorial membrane which may be histological evidence for other proposed mechanisms of cochlear toxicity in addition to membrane permeability alteration. The extent to which these effects occur partially depends on the concentration of aminoglycoside in the perilymph, which is the fluid that fills the scala tympani and scala vestibuli, allowing for direct contact with the organ of Corti.[10]

Federspil provides an analysis of the pharmacokinetics of aminoglycosides in perilymph. He found that by administering progressively larger systemic doses of aminoglycoside the concentration in perilymph increased in a linear fashion.[11] Federspil also demonstrated in the animal model that the terminal half-life of gentamicin in the perilymph was the same after chronic administration as it was after a single dose.[11] This suggests that fluctuation in serum concentrations, such as high peaks, does not contribute to accumulation in the perilymph and therefore may not directly affect the rate or extent of toxicity.[11]

From these findings, Federspil postulated that the total dose of aminoglycoside a patient receives is associated with the degree of cochlear damage.[12] Human clinical studies done in Baltimore on aminoglycoside ototoxicity further support this association.[12] One hundred thirty-five patients were studied for their relative risk of both reversible and irreversible auditory toxicity from aminoglycoside therapy. Using conventional audiometry, toxicity was ascribed if the patient had a loss of greater than or equal to 15 dB at any one frequency, determined by the comparison of pre- and post treatment audiograms. They found a 22.3% incidence of ototoxicity. Duration of therapy, total aminoglycoside dosage and bacteremia reached statistical significance as discriminators between the ototoxic and non-ototoxic groups.

Toxic aminoglycoside concentrations in the perilymph alone do not completely explain the occurrence or extent of ototoxicity. Studies have demonstrated that netilmicin and gentamicin are present in the same concentration in perilymph of guinea pigs and that their elimination rate is equivalent, but they do not produce the same incidence of toxicity.[12] Wersäll demonstrated that tobramycin in doses of 100mg/kg given for 18 days to guinea pigs produced more hair cell damage than therapeutically equivalent netilmicin given at the same dosage.[13] This has also been shown for netilmicin when compared to amikacin and gentamicin.[14] In comparison to these animal studies, results from human studies have been more controversial.

Wersäll reviewed the human comparative studies with the individual aminoglycosides and found problems in methodology, including not controlling for age, underlying disease and varying criterion for determining ototoxicity.[15] This renders comparisons of relative toxicities between the aminoglycosides difficult. The varying extent to which the individual aminoglycosides bind to various structures in the cochlea has not been adequately investigated but could provide helpful clues in determining relative ototoxic potentials.

Another difficulty in assessing aminoglycoside ototoxicity has been the lack of a clinically useful tool to measure pure tone hearing thresholds at frequencies greater than 8 kHz. New calibration and instrumentation techniques have aided in the development of high frequency audiometers. Fausti, in 1979, developed a technique that overcame some of the calibration concerns and still allowed for earphone testing.[16] Since then a new high frequency audiometer with which reproducible hearing thresholds can be obtained has become available.[17] Test-retest studies demonstrate that there is reliability in achieving reproducible results with this audiometer in clinical practice.[18] Studies establishing normal values have been performed but the firm establishment of the definition of normal hearing has not yet been determined.[18,19,20,21] This is partly due to varying methodology and instrumentation and is also largely due to the small numbers of ears tested to date.[22] A criterion for defining hearing loss secondary to ototoxicity is still debated due to a lack of normative data. Nevertheless, high-frequency audiometry is beginning to be used as a clinical tool for early detection of ototoxicity.

Using the calibration technique developed by Fausti, Dreschler et al. tested 100 ears of patients before and after receiving platinum derivatives and demonstrated a 68% incidence of hearing loss in the frequency range greater than 8 kHz, compared to a 44% incidence if only conventional audiometry had been used.[23] They defined hearing loss for their study as a threshold shift of 15 dB or more at any two frequencies, or 20 dB at one frequency. These findings support the use of high-frequency audiometry in the early detection of hearing loss from ototoxic agents that initially insult the basal portion of the cochlea.

OBJECTIVE

The purpose of this investigation was to evaluate cumulative effects of aminoglycoside therapy on high-frequency hearing thresholds. Specifically, the study evaluated whether or not differences in hearing thresholds could be detected between patients known to have received chronic aminoglycoside therapy versus those who have had no known exposure to ototoxic stimuli. This study design was similar to other investigations into noise-induced hearing loss in that one time audiograms of the patients were compared to single audiograms from normal individuals.[24,25]

A large number of cystic fibrosis patients are seen at the University of Utah and were considered an ideal population for an aminoglycoside ototoxicity study for many reasons. Patients with cystic fibrosis represent a relatively uniform population in terms of presentation of disease and the type of medical therapy required. Lung involvement accounts for greater than 95 percent of mortality associated with this disease.[26] The bacterial pneumonias which occur almost exclusively progress to involve <u>Pseudomonas aeruginosa</u> which is often susceptible to aminoglycosides. The majority of older cystic fibrosis patients therefore have required repeated therapy with these agents. Cystic fibrosis patients also represent a relatively young population, with the median life-span equal to about 19 years of age, and are accordingly less likely to have other reasons for hearing loss which would have excluded them from this study. Additionally, they are an ambulatory group in general, which allows for convenience in testing hearing. Finally, access to their complete medical records was possible in most cases because many of the patients have received treatment at the same institution for their entire life.

The purpose of this study was to identify any difference in mean hearing thresholds of cystic fibrosis patients who have received aminoglycosides repeatedly, when compared to those patients with cystic fibrosis who have not received any aminoglycoside and as compared to normal healthy volunteers. There is no evidence in the literature or by clinical observation to believe that hearing thresholds are different between individuals with cystic fibrosis and the rest of the population. This comparison was performed because the incidence of ototoxicity secondary to aminoglycoside treatment has not been adequately investigated in this population.

PATIENTS AND METHODS

Patients who were seen at the cystic fibrosis clinic at the University of Utah Medical Center were considered for participation. All patients with cystic fibrosis older than age six were considered for audiometric study. Responses in younger children may be unreliable due to inability to cooperate with testing procedures. Normal, healthy, age matched volunteers were used as controls. Subjects signed a consent form which along with our protocol was approved by the local institutional review board. All subjects were interviewed by the audiologist administering the test for factors known to contribute to hearing loss. This included history of head trauma, noise exposure, ear surgery, chronic ear infections, premature birth or family history of hearing loss. Only patients with a negative history of severe noise exposure or positive history of minor exposure followed by normal hearing thresholds at frequencies less than 8000 Hz that did not reflect noise exposure were used in the study. Patients whose medical histories were unknown or in question were also excluded from the investigation. A time period of at least two weeks from the last course of aminoglycoside therapy to the audiometric exam was required to reduce the detection of reversible toxicity.

The test site was the University of Utah Otolaryngology Clinic IAC model 403 sound-treated booth. Ambient noise levels were measured with a Larsen-Davis model 800B sound level meter and were well within the levels specified by the American National Standards Institute (ANSI) SC.1-1977.[27] These standards are not applicable to frequencies higher than 8000 Hz, but there was no measurable ambient noise in the frequencies above 8000 Hz. The test equipment included an Amplaid model 702 impedance bridge, a Grason-Stadler model 1704 clinical audiometer, and a Demlar model 20,000 Hz high-frequency audiometer. The Grason-Stadler audiometer was equipped with TDH-39 earphones in MX-41/AR cushions and was calibrated to ANSI S.3-1969 standards.[28] The Demlar audiometer was equipped with Koss model HV/1A earphones for which there are no ANSI specifications for calibration. The calibration for these earphones insured that the output at each frequency, in terms of dB sound-pressure-level (SPL), was the same as dial value. Frequency was measured and found to be within 3% of dial value. All calibration was accomplished using the Larson-Davis model 800 sound level meter (SLM) and associated 1/2 inch microphone, and the coupler described by Fausti et al.[18] Calibration was checked approximately every two months throughout the course of this study to insure accuracy of the stimuli.

To avoid any contamination of the data as a result of an underlying outer or middle ear dysfunction, an otoscopic examination was performed followed by tympanometry and acoustic reflex testing. Cerumen that obstructed visualization of the tympanic membrane was removed by an otolaryngology resident. Patients with abnormal tympanograms or absent acoustic reflexes were rescheduled for testing at a later date.

Pure-tone air-conduction thresholds were determined in both ears at 250 Hz, 500 Hz,1000 Hz,2000 Hz,3000 Hz, 4000 Hz, 6000 Hz, and 8000 Hz, using the conventional audiometer. Thresholds at frequencies from 8000 Hz to 20,000 Hz were determined at 1000 Hz intervals using the Demlar audiometer.(Appendix I) All thresholds were obtained using the procedure recommended by Carhart and Jerger.[29] Each subject was given conventional audiometric instructions and all audiometric testing was done by one of two professional audiologists holding the Certificate of Clinical Competence from the American Speech-Language-Hearing Association.

Descriptive statistics were used to represent the data. Paired t-tests were performed to evaluate any difference between the left and right ears, such that the data could be represented together if there was no difference noted. A level of confidence of 99% was used. Tests of significance were performed for each frequency where the number of subjects in each group was greater than ten. Since normal distribution is unlikely with a small number of subjects, non-parametric tests were utilized with a level of confidence of 95%. Subjects whose hearing threshold exceeded the maximum of the audiometer at any frequency were assigned a value of 99 dB for that frequency. For each frequency the number of ears that were assigned this value were recorded.

RESULTS

Thirty-eight patients with cystic fibrosis were evaluated audiometrically. Three patients were excluded from statistical analysis of hearing thresholds. One was excluded due to known concurrent severe noise exposure, one due to asymmetric loss in high frequencies in the left ear from unknown causes, and one due to persistently abnormal tympanometry after tympanic perforation. Thirty-eight normal subjects were studied. None of the subjects used as controls had a history of hearing loss, head trauma or severe noise exposure. The majority of the normal subjects worked at the hospital or were children of employees and were not considered experienced listeners. The patients and subjects were divided into six groups for analysis of effects of a positive history of aminoglycoside exposure on hearing threshold. Cystic fibrosis patients were divided into four groups based on the presence or absence of aminoglycoside exposure and age less than or greater than 20 years. Normal subjects were divided into two groups based on age. The mean age and number of patients and subjects per group is presented in Table A. It should be noted that there were only three subjects in the cystic fibrosis group that had not received aminoglycosides and were older than 20 years.

The Students paired, two-tailed t-test was performed using trimmed means to detect any difference between the left and right ear (Appendix II). A difference was noted at the 13,000 Hz frequency in the normal group, ($p < 0.01$). Because no other differences were noted, the data is represented with results from both ears combined. The mean hearing thresholds and standard deviations for each frequency are presented in Tables B1-4, categorized by group.

A comparison of the differences between groups was performed with one-tail Mann-Whitney *U* tests. To avoid the possibility of detecting a difference between groups at any frequency by chance alone from performing multiple tests, we limited the number of frequencies at which a comparison was made. Subject groups were compared at 4000 Hz, 6000 Hz, and 8000 Hz measured with the Grason-Stadler audiometer. Using the Demlar high-frequency audiometer groups were compared at 16,000 Hz, 17,000 Hz, 18,000 Hz, 19,000 Hz, and 20,000 Hz. These particular frequencies were chosen to compare the likelihood of finding elevations in hearing thresholds between the two ranges of audiometry testing.

There were no differences noted between cystic fibrosis patients who had not received drug therapy and the normal subjects when this test was applied to the data from the younger age group. (Table C) The data from the two groups were then combined and compared to those who had received drug. As displayed in Table D, differences were noted at the four highest frequencies in the younger age group (*p* <0.005), but not in the lower frequencies.

In the older age group there was an insufficient number of patients in the cystic fibrosis group who had never received aminoglycosides to perform inferential statistical analysis with this group separately. The patients were combined with normal subjects older than 20 years of age and compared to those who have received aminoglycoside to detect any statistically significant elevation in hearing threshold. The data were compared at the same frequencies as those listed with the younger age group. Differences were noted at all frequencies as represented in Table E. The level of significance was less than 0.001 at all of the lower frequencies and at 16,000 Hz and 17,000 Hz. The differences at frequencies 18000 Hz through 20,000 Hz reached significance at 0.005.

Table F refers to the number of patients who did not hear at the maximal output of the audiometer at various frequencies. For all frequencies, the number of patients who did not hear was greater in the groups who had received drug versus those who had not received drug. This is true for all frequencies except 19,000 Hz and 20,000 Hz in the older age group. In the older age group which had received drug, two patients had hearing deficits that extended into the frequencies below 15,000 Hz. Both had received prolonged courses of tobramycin extending 4 months in one and at least 9 months in the other.

Only one cystic fibrosis patient was noted to have a course of another possibly ototoxic agent. This patient had received one dose of furosemide one year prior to the audiogram, and had slightly elevated hearing thresholds when compared to normals in the high frequencies above 8000 Hz. The significance of this is not known.

DISCUSSION

There are limited data for normal hearing thresholds in the frequencies above 8000 Hz using the Demlar audiometer. Laukli and Mair used thirty medical students ages 20 to 24 for their normative data.[18] They found that some of their subjects did not respond to the 120 dB SPL maximal output of the audiometer, at frequencies above 16,000 Hz. This is consistent with the present findings, although our maximal output was set at 100 dB SPL. Laukli and Mair did not report mean and standard deviations for thresholds in this group, however it appears that their findings were similar to ours.

In 1979, Osterhammel and Osterhammel, used a different method of determining high frequency thresholds. They incorporated a quasi-freefield technique in a soundproof booth, tested the hearing of 286 normal subjects, 67 between the ages of 10 and 19, and 44 between the ages of 20 and 29.[21] High-frequency mean thresholds for their 10 to 19 year old age group were in good agreement with the finding of this study. The standard deviations ranged from 6.6 dB to 19.5 dB compared to our range of 5.9 dB to 21.7 dB, (see Table A). Note that the small standard deviations may be an erroneous finding in the highest frequencies because a large percentage of patients did not hear at the maximal output. The means and standard deviations for the older age group are also consistent with the present findings, with standard deviations ranging from 6.8 dB to 16.4 dB compared to 4.9 dB to 21.1 dB in this study.

Pedersen et al. used the data from the Osterhammel study to compare the chronic effects of tobramycin in cystic fibrosis patients.[30] Forty-six patients with cystic fibrosis were evaluated audiometrically using the same technique as they used in their normative study. Their criterion for determining hearing loss with one audiometric exam was not defined and it was not indicated whether or not they statistically compared the two groups to detect differences. They found two patients who had hearing loss that was attributed to tobramycin therapy. Of note, these two patients are the only patients found to have total hearing loss at some frequencies which is significantly different from findings in this study. It is possible that this discrepancy is due to the use of a lower decibel maximal output in this study.

There are certain limitations inherent in this study. The first is the inability to attribute the changes we found entirely to aminoglycoside exposure. A long-term prospective study that utilizes pre-treatment along with follow-up audiograms is necessary to identify aminoglycosides as the exclusive etiology for higher hearing thresholds. The second limitation is the inability to identify the extent to which aminoglycosides damage hearing over time. This would require an analysis of the total amount of each of the individual aminoglycosides received along with the time course the drug was delivered. Such a study is currently in progress at the University of Utah Medical Center. Thirdly, the sample size of each group was relatively small, restricting the power of the statistical analysis. Because of this it was not possible to statistically compare the older age group for differences in hearing thresholds, controlling for cystic fibrosis alone. Finally, it is important to note that elevation of pure tone hearing thresholds alone does not define hearing loss. Also, since normal pure tone thresholds are not defined above 8000 Hz, one cannot say with complete certainty that the aminoglycoside groups had ototoxicity. They do, however, demonstrate reduced hearing sensitivity in the extended high frequency range.

Particularly in patients aged between 10 and 19 years, these findings suggest that high-frequency audiometry does serve as a useful tool in detecting early damage due to ototoxicity. Mean and individual thresholds measured by conventional audiometry do not indicate threshold shifts in this age group.

It is helpful to contrast these findings in the younger ages to those in the older age group, where elevations of hearing thresholds are seen at all the frequencies tested. For the majority of cystic fibrosis patients older than 20 years of age, the persistance of pulmonary dysfunction increases the likelihood that they have received extensive aminoglycoside therapy. High-frequency audiometry would seem to be less useful as an initial screening tool in these patients.

In summary we found that patients with cystic fibrosis aged 10 through 19 years, who have received aminoglycoside have increased mean hearing thresholds in the frequencies, 16,000 Hz through 20,000 Hz. There was no difference in mean hearing thresholds between cystic fibrosis patients who had not recieved aminoglycoside treatment and normal healthy volunteers. For those cystic fibrosis patients older than 20 years, higher mean hearing thresholds for all frequencies tested were noted when compared to normal subjects.

TABLES

TABLE A. Mean age and number of patients/subjects in each group.

GROUP	number =	MEAN AGE
cystic fibrosis (C.F.)		
age 6-19 years:		
aminoglycoside	12	13.2
no drug	10	10.4
age 20 + years:		
aminoglycoside	10	25.4
no drug	3	25.3
normals		
age 6-19 years	18	11.2
age 20 + years	20	25.5
combined groups		
age 6-19 years:		
C.F. no drug + normal	28	10.9
age 20 + years:		
C.F. no drug + normal	23	25.4

Table B-1. **Mean pure tone hearing thresholds for conventional frequencies. Standard deviations are in parentheses.**

	CYSTIC FIBROSIS PATIENTS			
AGE (years)	6-19	6-19	>20	>20
AMINOGLYCOSIDE EXPOSURE	YES	NO	YES	NO
NUMBER (ears)	24	20	20	6
250 Hz (HTL)	13.8 (6.5)	13.3 (6.1)	15.3 (4.1)	14.2 (3.8)
500 Hz	11.0 (7.2)	9.0 (6.8)	12.8 (6.6)	8.3 (7.5)
1000 Hz	4.6 (5.9)	3.3 (6.0)	10.0 (13.8)	3.3 (4.1)
2000 Hz	4.2 (6.0)	3.0 (7.2)	18.2 (28.7)	1.7 (2.6)
3000 Hz	3.1 (7.0)	1.0 (7.9)	16.0 (30.4)	7.5 (6.9)
4000 Hz	2.9 (5.9)	3.5 (6.5)	19.7 (28.1)	14.2 (9.7)
6000 Hz	9.0 (8.7)	6.8 (9.6)	28.0 (29.1)	25.8 (15.3)
8000 Hz	10.6 (8.2)	8.5 (9.1)	27.0 (30.3)	11.7 (13.1)

HTL = hearing threshold level

Table B-2. Mean pure tone hearing thresholds for conventional frequencies. Standard deviations are in parentheses.

	NORMAL SUBJECTS	
AGE (years)	6-19	>20
NUMBER (ears)	36	40
250 Hz (HTL)	11.1	9.5
	(5.8)	(7.1)
500 Hz	9.1	6.6
	(6.2)	(6.2)
1000 Hz	3.2	2.4
	(5.1)	(4.7)
2000 Hz	1.1	1.5
	(3.8)	(5.1)
3000 Hz	3.5	2.5
	(4.4)	(6.7)
4000 Hz	4.4	3.5
	(5.6)	(8.2)
6000 Hz	8.5	8.9
	(5.8)	(9.2)
8000 Hz	9.0	5.8
	(8.9)	(8.9)

HTL = hearing threshold level

Table B-3. Mean pure tone hearing thresholds at frequencies above 8000 Hz. Standard deviations are in parentheses.

	CYSTIC FIBROSIS PATIENTS			
AGE (years)	6-19	6-19	>20	>20
AMINOGLYCOSIDE EXPOSURE	YES	NO	YES	NO
NUMBER (ears)	24	20	20	6
8000 Hz (SPL)	23.5	22.8	42.9	21.6
	(6.0)	(7.7)	(24.4)	(12.5)
9000 Hz	27.9	26.0	42.2	36.7
	(6.7)	(11.2)	(30.4)	(12.5)
10000 Hz	26.3	23.5	39.2	43.3
	(8.6)	(8.0)	(31.3)	(14.4)
11000 Hz	25.2	25.5	42.6	50.8
	(8.3)	(9.2)	(29.9)	(27.3)
12000 Hz	27.3	28.8	46.1	56.7
	(10.7)	(8.7)	(29.0)	(28.2)
13000 Hz	37.3	33.3	54.1	65.0
	(13.6)	(10.7)	(25.9)	(27.4)
14000 Hz	37.3	32.0	59.6	66.7
	(17.9)	(13.2)	(25.7)	(18.6)
15000 Hz	42.3	33.8	66.3	65.8
	(22.2)	(13.7)	(25.2)	(19.9)
16000 Hz	54.7	48.3	82.4	77.3
	(20.6)	(15.6)	(17.8)	(20.0)
17000 Hz	67.8	55.5	90.2	86.2
	(16.6)	(15.3)	(13.0)	(16.8)
18000 Hz	80.0	68.0	95.6	94.3
	(15.9)	(17.0)	(6.0)	(7.2)
19000 Hz	89.8	76.6	98.1	99.0
	(14.2)	(17.3)	(2.8)	(0.0)
20000 Hz	94.3	82.0	98.0	99.0
	(10.6)	(16.9)	(2.9)	(0.0)

SPL = sound pressure level

Table B-4. Mean pure tone hearing thresholds (standard deviation) at frequencies above 8000 Hz.

NORMAL SUBJECTS

AGE (years)	6-19	>20
NUMBER (ears)	36	40
8000 Hz (SPL)	21.8 (7.4)	21.4 (6.7)
9000 Hz	24.3 (7.0)	23.3 (8.6)
10000 Hz	21.4 (7.3)	20.6 (9.1)
11000 Hz	22.9 (6.5)	26.0 (12.8)
12000 Hz	22.9 (5.9)	25.6 (12.9)
13000 Hz	26.1 (6.8)	36.2 (16.2)
14000 Hz	31.0 (10.1)	40.6 (18.8)
15000 Hz	41.1 (17.7)	48.2 (21.1)
16000 Hz	50.0 (21.0)	60.5 (21.0)
17000 Hz	57.5 (20.7)	73.1 (19.0)
18000 Hz	69.6 (21.7)	85.5 (15.2)
19000 Hz	80.7 (19.2)	92.3 (11.0)
20000 Hz	85.8 (15.1)	95.1 (4.9)

SPL = sound pressure level

Table C. p values for age group 6 to 19, comparison between cystic fibrosis patients with no drug exposure and normal volunteers, using the Mann-Whitney U one tail test.

CYSTIC FIBROSIS (n = 20) and NORMAL SUBJECTS (n = 36)

frequency:	$p <$
4000 Hz	0.209
6000 Hz	0.205
8000 Hz	0.496
17000 Hz	0.496
18000 Hz	0.395
19000 Hz	0.156
20000 Hz	0.231

n = number of ears

Table D. *p* values for age group 6 to 19, comparison between cystic fibrosis patients with drug exposure and cystic fibrosis patients with no drug exposure combined with normal volunteers using the one-tail Mann-Whitney *U* test.

CYSTIC FIBROSIS (+ DRUG) and	CYSTIC FIBROSIS (NO DRUG)
(n = 24)	with NORMAL SUBJECTS (n = 56)

frequency:	$p <$
4000 Hz	0.189
6000 Hz	0.282
8000 Hz	0.134
17000 Hz	0.005
18000 Hz	0.009
19000 Hz	0.006
20000 Hz	0.00005

n = number of ears

Table E. *p* values for age group 20 and older, comparison between cystic fibrosis patients with drug exposure and cystic fibrosis patients with no drug exposure combined with normal volunteers, using the one-tail Mann-Whitney *U* test.

CYSTIC FIBROSIS (+ DRUG) (n = 20)	and	CYSTIC FIBROSIS (NO DRUG) with NORMAL SUBJECTS (n = 46)

frequency:	p <
4000 Hz	0.001
6000 Hz	0.0006
8000 Hz	0.0001
17000 Hz	0.0007
18000 Hz	0.002
19000 Hz	0.004
20000 Hz	0.002

n = number of ears

TABLE F. Number/percentage of patients and subjects that did not hear at 100db.

DISEASE	CYSTIC FIBROSIS				NORMAL SUBJECTS	
DRUG	YES	NO	YES	NO	NO	NO
AGE GROUP	6-19	6-19	)20	)20	6-19	)20
n =	12	10	10	3	18	20
250 Hz						
500 Hz						
1000 Hz						
2000 Hz						
3000 Hz			1/5%			
4000 Hz			1/5%			
6000 Hz			1/5%			
8000 Hz			1/5%			
8000 Hz spl			2/10%			
9000 Hz			2/10%			
10000 Hz			2/10%			
11000 Hz			2/10%			
12000 Hz			2/10%			
13000 Hz			4/20%			
14000 Hz			4/20%			
15000 Hz			5/25%			
16000 Hz	1/4.2%		7/35%	1/16.6%	1/2.8%	4/10%
17000 Hz	3/12.5%		12/60%	2/33.3%		5/12.5%
18000 Hz	4/16.6%	1/5%	12/65%	3/50%	3/8.3%	8/20%
19000 Hz	8/33.3%	3/15%	14/70%	6/100%	9/25%	18/45
20000 Hz	11/45.8%	5/25%	14/70%	6/100%	5/13.9%	17/42.5%

n = number of patients/subjects; spl = sound pressure level

APPENDIX I

Individual pure tone hearing thresholds in decibels for:
CYSTIC FIBROSIS PATIENTS: 6-19 years age group
aminoglycoside

PATIENT NUMBER	SEX MALE =T FEMALE=F	Hz 250 L	250 R	500 L	500 R	1k L	1k R	2k L	2k R	3k L	3k R	4k L	4k R	6k L	6k R	8k L	8k R	SPL 8k L	8k R
3	.T.	15	10	10	10	0	5	-5	5	10	15	0	5	0	5	5	10	25	10
7	.T.	20	25	20	25	5	10	10	5	10	5	10	10	10	10	15	15	20	15
8	.T.	10	10	10	10	0	0	0	0	-5	-5	5	10	-5	5	5	0	20	0
9	.T.	5	10	5	5	0	0	0	0	0	0	0	0	25	15	20	15	25	15
11	.T.	15	15	15	20	10	15	15	20	15	15	10	15	15	15	35	10	35	10
27	.T.	15	15	10	15	5	5	0	5	0	5	-5	0	20	15	10	5	25	5
20	.F.	15	20	10	15	0	5	0	5	0	5	5	5	25	10	15	10	30	10
26	.F.	5	10	0	-5	-5	-5	0	0	-5	5	-10	-5	0	0	0	10	25	10
33	.T.	25	25	15	25	15	15	5	10	5	10	5	0	10	5	15	5	25	5
34	.F.	10	20	10	10	5	5	5	0	-10	-5	0	0	-10	0	5	0	15	0
35	.T.	10	15	10	0	0	0	5	-5	5	-5	0	0	10	10	10	5	20	5
36	.F.	10	0	10	10	10	10	10	10	5	0	0	10	15	10	25	10	20	10

Individual pure tone hearing thresholds in decibels for:
CYSTIC FIBROSIS PATIENTS: 6-19 years age group
aminoglycoside

PATIENT NUMBER	SEX MALE =T FEMALE=F	kHz	9k L	9 R	10 L	10 R	11 L	11 R	12 L	12 R	13 L	13 R	14 L	15 R	16 L	16 R	17 L	17 R	18 L	18 R	19 L	19 R	20 L	20 R
3	.T.		25	35	25	25	30	25	30	25	35	35	25	40	50	50	60	70	70	85	85	95	85	99
7	.T.		30	35	40	45	35	35	45	40	45	60	60	99	80	99	85	99	95	99	99	99	99	99
8	.T.		20	20	15	15	20	20	15	30	30	40	35	30	55	40	85	60	99	65	99	90	99	95
9	.T.		40	30	25	20	20	15	20	20	20	25	15	35	35	40	45	50	45	50	50	50	65	60
11	.T.		35	30	35	35	40	25	40	30	45	30	45	30	45	50	60	70	80	85	90	95	99	99
27	.T.		30	35	35	35	25	15	20	15	30	20	20	25	40	50	55	65	80	85	95	95	99	99
20	.F.		25	25	20	20	20	15	20	20	25	35	30	30	45	40	50	50	60	55	85	70	99	85
26	.F.		35	30	25	35	25	30	35	20	30	30	35	40	50	30	65	55	90	80	99	95	99	99
33	.T.		20	15	25	20	25	50	40	55	50	65	45	65	75	75	90	70	99	99	99	99	99	99
34	.F.		20	20	25	30	20	25	15	20	25	25	20	15	45	40	55	70	75	75	95	80	95	95
35	.T.		30	30	20	30	25	20	25	15	45	30	35	35	45	40	60	60	75	85	99	99	99	99
36	.F.		20	35	10	20	25	20	30	30	65	55	90	80	99	95	99	99	99	90	95	99	99	99

Individual pure tone hearing thresholds in decibels for:
CYSTIC FIBROSIS PATIENTS: 6-19 years age group
no aminoglycoside

PATIENT NUMBER	SEX MALE =T FEMALE=F	Hz	250 L	250 R	500 L	500 R	1k L	1k R	2k L	2k R	3k L	3k R	4k L	4k R	6k L	6k R	8k L	8k R	SPL	8k L	8k R
2	.F.		10	15	5	15	5	10	0	0	5	5	10	10	20	20	25	30		35	30
5	.T.		5	10	5	10	0	5	10	5	-5	-5	0	5	5	10	0	5		15	5
6	.T.		20	15	10	20	5	5	0	5	0	5	0	5	25	10	10	15		20	15
12	.T.		20	25	10	10	-5	0	-5	0	-5	-5	-5	-5	-5	-5	0	5		25	5
13	.T.		10	10	0	0	0	-10	0	0	0	10	-5	5	-10	0	-10	5		5	5
21	.F.		10	0	5	0	5	0	0	0	0	-5	0	0	5	15	10	10		15	10
30	.F.		10	10	10	10	0	5	-10	0	5	5	5	5	10	5	5	0		15	0
31	.T.		15	15	5	15	5	0	10	10	-5	0	10	5	5	0	10	5		30	5
32	.F.		10	15	0	10	0	5	-5	5	-10	-10	-5	0	0	-5	10	5		30	5
37	.F.		15	25	15	25	15	15	15	20	15	20	10	20	15	15	10	20		30	20

Individual pure tone hearing thresholds in decibels for:
CYSTIC FIBROSIS PATIENTS: 6-19 years age group
no aminoglycoside

PATIENT NUMBER	SEX MALE =T FEMALE=F	kHz	9k L	9 R	10 L	10 R	11 L	11 R	12 L	12 R	13 L	13 R	14 L	15 R	16 L	16 R	17 L	17 R	18 L	18 R	19 L	19 R	20 L	20 R
2	.F.		40	35	25	25	20	20	35	25	45	25	40	30	50	70	65	80	70	99	99	99	99	99
5	.T.		15	20	15	20	15	20	20	30	25	30	20	55	40	80	45	90	65	95	85	90	90	90
6	.T.		30	50	25	35	30	25	35	25	30	35	25	25	35	40	60	50	70	70	75	75	99	80
12	.T.		20	25	25	15	25	15	45	35	30	70	35	70	55	70	60	65	75	75	90	85	99	90
13	.T.		5	15	15	25	20	30	30	40	35	45	30	30	45	45	60	55	80	75	80	85	85	90
21	.F.		35	25	10	10	25	10	15	10	30	30	15	15	30	20	35	30	35	50	55	50	60	60
30	.F.		15	25	20	30	25	30	25	35	30	35	35	40	40	55	50	40	50	45	60	50	65	55
31	.T.		40	15	40	20	40	15	35	20	25	20	20	25	35	30	45	35	65	45	75	45	90	45
32	.F.		30	15	30	30	45	30	35	20	30	25	25	25	55	70	60	75	85	85	99	95	99	95
37	.F.		35	30	25	30	30	40	30	30	35	35	40	50	50	50	55	55	60	65	70	70	75	75

Individual pure tone hearing thresholds in decibels for:
NORMAL SUBJECTS: 6-19 years age group

SUBJECT NUMBER	SEX MALE =T FEMALE=F	Hz 250 L	250 R	500 L	500 R	1k L	1k R	2k L	2k R	3k L	3k R	4k L	4k R	6k L	6k R	8k L	8k R	SPL 8k L	8k R
17	.F.	25	25	25	25	15	20	5	0	5	0	5	0	10	10	5	15	20	15
18	.F.	10	5	5	5	5	0	0	0	0	0	5	0	5	15	5	15	5	15
25	.F.	10	5	10	10	5	10	5	5	5	0	5	0	20	10	30	35	35	35
19	.F.	10	10	0	15	0	-5	5	0	5	0	-5	-5	5	5	5	0	20	0
31	.F.	10	10	10	10	0	0	10	0	5	5	10	5	15	10	20	5	20	5
8	.F.	10	5	5	5	5	5	5	0	0	5	0	5	-5	5	0	0	20	0
26	.F.	20	5	15	10	0	5	0	0	0	10	0	5	0	5	0	10	15	10
28	.F.	5	10	5	10	0	5	-5	0	-5	5	-5	5	0	5	5	5	25	5
27	.F.	15	10	5	15	0	5	-5	5	5	0	5	5	10	10	5	5	25	5
29	.F.	5	5	5	10	0	0	0	5	5	5	5	0	15	10	0	0	20	0
11	.F.	10	15	10	10	0	10	0	0	0	0	10	5	10	15	5	5	15	5
12	.F.	10	10	5	10	0	5	-5	-5	0	0	0	5	0	5	-5	10	15	10
13	.F.	20	15	10	15	0	0	-5	5	0	5	-10	10	15	10	10	5	20	5
32	.F.	15	20	5	15	5	5	5	0	5	10	5	5	5	15	20	15	35	15
33	.T.	0	5	-5	0	0	5	0	0	0	5	10	10	5	10	10	0	25	0
34	.F.	15	10	5	5	0	0	0	-5	10	15	15	10	15	5	15	15	25	15
3	.T.	10	10	5	5	0	-5	5	5	10	5	15	10	10	5	5	10	20	10
4	.F.	15	10	15	15	10	5	5	0	10	-5	5	10	2	20	25	15	35	15

Individual pure tone hearing thresholds in decibels for:
NORMAL SUBJECTS: 6-19 years age group

SUBJECT NUMBER	SEX MALE =T FEMALE=F	kHz	9k L	9 R	10 L	10 R	11 L	11 R	12 L	12 R	13 L	13 R	14 L	15 R	16 L	16 R	17 L	17 R	18 L	18 R	19 L	19 R	20 L	20 R
17	.F.		25	25	20	15	35	30	25	30	35	40	50	85	99	95	95	99	99	95	99	95	99	95
18	.F.		15	30	20	25	25	25	25	25	30	20	35	30	35	30	45	30	45	40	40	40	50	45
25	.F.		40	35	35	30	25	20	15	15	25	20	20	15	40	20	50	45	65	60	70	70	75	70
19	.F.		25	10	25	10	25	10	30	15	35	20	20	25	25	25	30	30	35	35	40	45	45	65
31	.F.		20	20	15	15	10	25	15	25	20	35	25	25	65	30	70	35	75	35	80	70	85	85
8	.F.		25	20	25	25	30	20	25	25	20	20	20	40	30	40	40	35	40	40	65	75	90	95
26	.F.		20	20	20	10	20	15	20	10	25	15	30	30	30	30	35	45	70	70	90	90	90	90
28	.F.		35	35	35	35	30	25	20	30	35	25	40	50	80	60	90	65	95	99	99	99	95	95
27	.F.		25	20	25	10	30	25	25	25	35	25	40	45	35	50	50	45	80	60	95	85	95	95
29	.F.		35	25	20	20	25	25	25	25	25	30	25	45	45	60	45	70	80	95	99	99	99	95
11	.F.		15	25	20	20	15	25	20	25	25	25	30	30	65	40	50	50	95	65	99	90	99	90
12	.F.		25	20	35	25	30	25	35	25	25	25	25	55	75	70	75	75	90	90	99	90	95	95
13	.F.		30	25	35	20	40	20	30	10	35	30	30	30	60	40	95	50	99	55	99	60	99	70
32	.F.		20	30	15	20	20	25	20	25	20	15	25	30	35	45	55	60	70	65	75	70	80	75
33	.T.		25	20	15	15	20	15	15	15	25	20	40	30	40	35	50	35	50	50	70	90	80	90
34	.F.		35	20	15	25	20	15	25	25	30	20	30	25	50	35	65	40	60	50	75	55	90	85
3	.T.		15	15	15	15	15	20	25	25	35	35	55	70	80	85	80	95	95	95	99	99	95	95
4	.F.		30	20	25	20	25	20	30	25	25	15	30	35	60	60	70	75	75	90	90	99	99	99

Individual pure tone hearing thresholds in decibels for:
CYSTIC FIBROSIS PATIENTS:)= 20 years age group
aminoglycoside

PATIENT NUMBER	SEX MALE =T FEMALE=F	Hz 250 L	250 R	500 L	500 R	1k L	1k R	2k L	2k R	3k L	3k R	4k L	4k R	6k L	6k R	8k L	8k R	SPL 8k L	8k R
1	.T.	10	10	10	10	5	5	20	20	25	25	10	20	25	20	10	10	30	10
4	.F.	15	5	15	5	5	5	0	0	-10	-10	5	0	10	10	10	0	20	0
14	.F.	20	15	15	10	0	5	10	5	15	0	10	10	15	30	25	35	45	35
18	.T.	15	15	5	0	-5	0	0	0	0	-10	0	0	20	0	10	-10	35	-10
23	.F.	15	15	10	15	10	10	10	0	5	5	20	20	15	15	15	10	35	10
29	.F.	15	15	25	15	15	10	25	20	10	0	20	15	80	15	80	20	90	20
25	.T.	20	15	15	15	10	10	15	10	15	5	15	5	15	15	25	25	40	25
17	.F.	20	10	10	10	5	5	10	5	5	0	5	5	10	15	10	15	25	15
24	.T.	15	20	10	15	5	5	10	5	20	20	20	15	35	15	30	20	45	20
38	.F.	20	20	15	30	40	55	99	99	99	99	99	99	99	99	99	99	99	99

Individual pure tone hearing thresholds in decibels for:
CYSTIC FIBROSIS PATIENTS:)= 20 years age group
no aminoglycoside

PATIENT NUMBER	SEX MALE =T FEMALE=F	Hz 250 L	250 R	500 L	500 R	1k L	1k R	2k L	2k R	3k L	3k R	4k L	4k R	6k L	6k R	8k L	8k R	SPL 8k L	8k R
10	.F.	10	10	5	5	0	5	0	5	0	0	5	5	15	20	0	5	20	5
15	.T.	20	15	20	15	0	10	5	0	10	5	10	20	45	40	30	25	35	25
16	.T.	15	15	0	5	5	0	0	0	15	15	15	30	5	30	10	0	10	0

Individual pure tone hearing thresholds in decibels for:
CYSTIC FIBROSIS PATIENTS:)= 20 years age group
aminoglycoside

PATIENT NUMBER	SEX MALE =T FEMALE=F	9k L	9 R	10 L	10 R	11 L	11 R	12 L	12 R	13 L	13 R	14 L	15 R	16 L	16 R	17 L	17 R	18 L	18 R	19 L	19 R	20 L	20 R
1	.T.	25	10	10	5	15	15	15	20	30	40	40	35	65	50	70	60	80	85	90	90	90	90
4	.F.	35	25	10	25	30	15	25	25	25	30	35	25	60	55	90	70	90	85	99	99	99	95
14	.F.	25	25	10	25	25	30	35	30	40	45	40	55	70	90	70	99	95	99	99	99	99	99
18	.T.	15	20	20	15	15	20	20	25	30	25	35	60	75	75	90	85	90	99	99	99	99	99
23	.F.	30	30	40	45	45	30	45	35	60	50	80	80	99	99	99	99	99	99	99	99	99	99
29	.F.	95	95	95	90	99	95	99	95	99	99	99	99	99	99	99	99	99	99	99	99	99	99
25	.T.	65	50	45	40	40	35	45	40	70	55	75	65	95	90	99	99	99	99	99	99	99	99
17	.F.	25	25	30	30	40	40	45	35	45	55	55	75	95	99	99	99	99	99	99	99	99	99
24	.T.	25	25	25	25	40	25	65	25	50	35	55	40	80	55	99	80	99	99	99	99	99	99
38	.F.	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99

Individual pure tone hearing thresholds in decibels for:
CYSTIC FIBROSIS PATIENTS:)= 20 years age group
no aminoglycoside

PATIENT NUMBER	SEX MALE =T FEMALE=F	9k L	9 R	10 L	10 R	11 L	11 R	12 L	12 R	13 L	13 R	14 L	15 R	16 L	16 R	17 L	17 R	18 L	18 R	19 L	19 R	20 L	20 R
10	.F.	30	35	35	45	30	35	30	55	50	55	50	75	90	99	99	99	99	99	99	99	99	99
15	.T.	60	40	70	45	85	85	90	85	95	95	85	95	75	90	90	99	99	99	99	99	99	99
16	.T.	30	25	30	35	25	45	20	60	25	70	55	50	65	45	65	65	85	85	99	99	99	99

Individual pure tone hearing thresholds in decibels for:
NORMAL SUBJECTS:)= 20 years age group

SUBJECT NUMBER	SEX MALE =T FEMALE=F	Hz 250 L	250 R	500 L	500 R	1k L	1k R	2k L	2k R	3k L	3k R	4k L	4k R	6k L	6k R	8k L	8k R	SPL 8k L	8k R
23	.F.	20	15	10	5	5	5	5	10	15	5	15	5	10	10	15	20	15	20
21	.F.	0	5	10	5	0	0	0	0	0	-10	0	-5	5	-5	10	5	20	5
36	.F.	10	20	10	-5	10	0	15	-5	20	-5	15	-5	20	0	10	5	15	5
14	.F.	15	15	5	10	0	5	0	0	0	5	0	10	5	10	0	0	20	0
15	.F.	15	20	5	30	5	15	0	5	0	10	0	5	5	10	5	5	15	5
16	.F.	10	10	10	10	0	5	5	0	-10	-5	5	0	5	10	-10	10	10	10
35	.F.	15	10	5	15	-5	0	5	0	5	5	15	0	15	5	5	10	25	10
37	.F.	15	15	10	10	0	5	10	0	20	0	25	10	15	15	10	5	15	5
10	.F.	10	10	10	10	0	0	0	0	5	0	0	0	0	-10	-5	-5	10	-5
6	.F.	10	5	10	5	0	5	5	0	0	0	5	0	10	10	20	10	30	10
1	.F.	0	10	0	0	-5	-5	-10	-5	5	-5	-5	-5	5	-5	-10	-5	25	-5
22	.F.	5	5	0	5	5	0	0	0	0	0	0	5	5	10	0	0	15	0
30	.F.	10	10	5	0	0	0	5	5	2	0	10	15	15	20	20	15	25	15
7	.F.	-10	-10	-5	-5	0	5	0	5	0	0	-5	-5	5	0	5	5	25	5
9	.F.	0	5	5	10	5	15	5	5	-5	-5	5	5	10	15	5	15	20	15
38	.F.	10	10	5	5	0	5	0	5	5	5	-5	5	5	10	5	5	20	5
2	.F.	10	5	10	5	-5	-5	-10	-10	10	5	5	-5	15	0	10	-5	20	-5
24	.F.	10	20	0	5	5	5	5	5	0	10	-5	10	35	20	30	15	30	15
20	.F.	10	10	10	15	5	5	0	0	10	5	25	-10	35	5	0	-10	30	-10
5	.T.	20	15	10	5	0	0	5	0	0	0	0	0	0	0	5	0	25	0

Individual pure tone hearing thresholds in decibels for:
NORMAL SUBJECTS:)= 20 years age group

SUBJECT NUMBER	SEX MALE =T FEMALE=F	kHz 9k L	9 R	10 L	10 R	11 L	11 R	12 L	12 R	13 L	13 R	14 L	15 R	16 L	16 R	17 L	17 R	18 L	18 R	19 L	19 R	20 L	20 R
23	.F.	30	30	10	25	10	15	25	20	25	30	35	30	35	35	55	50	70	70	90	80	90	95
21	.F.	25	20	15	15	15	10	10	5	20	20	20	25	60	35	75	65	85	95	95	90	95	90
36	.F.	30	20	25	30	30	25	40	25	60	35	40	40	60	40	85	70	90	85	99	90	99	99
14	.F.	30	25	15	20	30	25	25	25	30	25	40	50	60	70	70	70	90	90	99	99	99	99
15	.F.	15	45	20	10	25	15	25	15	25	15	20	35	35	30	35	45	50	60	60	85	95	90
16	.F.	35	35	10	10	30	25	20	15	25	25	30	30	50	50	55	60	95	90	99	99	95	99
35	.F.	25	15	20	25	25	35	25	30	30	30	30	40	60	55	55	60	65	60	99	99	95	99
37	.F.	15	25	50	30	70	50	70	40	75	60	80	90	99	99	99	99	99	99	99	99	99	99
10	.F.	20	15	0	20	10	10	10	10	30	20	30	25	15	25	30	40	45	50	55	60	80	85
6	.F.	20	10	20	25	15	20	35	35	55	50	65	75	80	70	85	99	95	99	99	99	99	99
1	.F.	20	15	10	25	20	20	25	20	50	65	45	75	70	80	85	95	90	99	95	99	99	99
22	.F.	25	20	25	20	25	25	15	15	25	20	30	45	60	75	90	85	99	95	99	95	99	99
30	.F.	20	30	25	25	35	40	45	50	70	65	75	95	99	99	99	99	99	99	99	99	99	99
7	.F.	30	25	25	25	30	25	25	30	45	35	45	45	60	60	70	90	90	95	90	95	99	95
9	.F.	25	40	15	25	10	25	15	15	20	15	50	70	65	70	75	70	80	80	85	90	90	90
38	.F.	25	0	40	30	50	30	50	35	50	35	50	45	85	70	99	80	99	99	99	99	99	99
2	.F.	20	15	20	15	30	30	20	20	35	30	25	50	65	65	75	70	90	85	90	95	85	99
24	.F.	30	10	20	30	45	40	35	30	40	40	45	40	70	50	85	55	99	90	99	99	95	95
20	.F.	25	25	15	10	20	25	20	20	20	25	20	30	70	35	75	80	90	85	95	95	90	95
5	.T.	30	15	20	10	10	15	15	20	30	45	40	50	40	70	55	90	80	95	85	95	90	90

APPENDIX II

Trimmed two tail t-test statistics: Evaluation of differences between left and right ears for individual frequencies.

	NORMAL SUBJECTS		CYSTIC FIBROSIS	
sample size =	38		35	
FREQUENCY	t-STAT.	*P*-VALUE	t-STAT.	*P*-VALUE
250 hZ	-0.17	0.87	-0.15	0.88
500	-2.19	0.04	-1.58	0.12
1000	-2.27	0.03	-2.20	0.04
2000	0.46	0.65	0.15	0.89
3000	1.08	0.29	0.44	0.67
4000	0.92	0.37	-2.44	0.02
6000	1.18	0.25	0.87	0.39
8000	0.68	0.50	2.00	0.05
8000 (HFA)	-0.26	0.80	0.71	0.48
9000	1.90	0.07	0.78	0.44
10000	0.64	0.53	-0.97	0.34
11000	1.88	0.07	1.08	0.29
12000	2.15	0.04	0.50	0.62
13000	3.24	0.01	-0.93	0.36
14000	0.84	0.40	-0.79	0.43
15000	0.96	0.34	-1.00	0.32
16000	2.25	0.03	-1.13	0.27
17000	1.48	0.15	-0.64	0.53
18000	1.78	0.08	-1.03	0.31
19000	1.00	0.33	1.86	0.07
20000	-0.18	0.86	2.24	0.03

HFA = high frequncy audiometry

APPENDIX III

INFORMED CONSENT

HIGH FREQUENCY HEARING IN PATIENTS WITH CYSTIC FIBROSIS RECEIVING AMINOGLYCOSIDE THERAPY

You are being asked to participate in a study that will involve testing your hearing. You may have received antibiotics that belong to a group called aminoglycosides. These agents have been known to cause hearing loss. The reason we want to perform this study is to see if we can find out if the total amount of aminoglycoside you have ever received has anything to do with your hearing.

The hearing test will involve sitting in a sound-proof room with earphones on and listening to some tones. You will just let the person testing your hearing know when you hear the sounds. The test is painless and cannot harm you. The person who does the test will explain to you what he finds out about your hearing when the test is over. Depending upon your age, the whole process should take around 45 minutes to 1 hour. The testing will take place in clinic 9 of the University hospital.

When you receive your hearing test, a middle ear infection may be noticed, even though you have no pain in your ears. Even though this infection may not bother you it may change your hearing test results. If this should happen to you, you will be asked to have the test repeated the next time you return to clinic or in approximately two to three weeks. It is important to test your hearing when you do not have any ear infection.

If you have ever received aminoglycosides we will also look through your medical records to find out how much of these drugs you have received in your lifetime.

Every effort will be made to keep all of your records private to protect your identity. In the event that this research is published, your name will not be used.

If you have any questions at this time, please feel free to ask them. If you decide to participate in the study and have any questions at a later time, you should contact Teresa McRorie, R.Ph. or John Bosso, Pharm.D. at 581-5984.

If you have any questions regarding this study which you would rather not discuss with the people who are performing the project, you are are free to call the office of the Institutional Review Board, 581-3655.

I understand that participation in this study is my own choice and that I may decide not to participate at any time. If I decide not to participate, it will not affect the quality of care that I receive. A copy of this consent form has been given to me.

______________________________ __________________
Patient Date

______________________________ __________________
Parent or Guardian Witness

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